(iv) multipotent colony-forming cells ~~(CFC-GEMM)~~, and

(v) immature lymphoid precursor cells;

(b) [recognizing an] which antigen is present on a maximum of about 5% non-malignant, human marrow cells and a maximum of about 1% non-malignant, human peripheral blood cells; and

(c) [not recognizing an] which antigen is not present on non-malignant, mature human myeloid and lymphoid cells.

2~~4~~. (Amended) The monoclonal antibody of claim [3] 2 that corresponds to the monoclonal antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483.

3~~5~~. (Amended) The monoclonal antibody of claim [3] 2 that is the antibody produced by the hybridoma deposited under ATCC Accession No. HB-8483.

REMARKS

In order to more clearly define the invention, claim 2 has been amended to incorporate the language of originally filed claim 3. The amendments to claim 2 serve to emphasize that the claimed antibody is defined in terms of the antigen it recognizes. The claim scope encompasses monoclonal antibodies which are reactive with a unique antigen, identified by the deposited hybridoma and found on immature human cells capable of differentiating into five different myeloid or lymphoid cell types but not found on mature human blood or bone marrow cells. The present inventor discovered that such an antigen exists.

Claim 1 has been cancelled in favor of amended claim 2 which, as noted above, more completely characterizes the invention. Claims 3, 6 and 8 have been cancelled, and claims 4 and 5 have been amended, solely to ensure proper dependency of the claims.

The Interview

Applicant wishes to thank Examiner Cunningham and Examiner Kushan for the courtesy of an interview. At the interview, Applicant proposed the above amendments to the claims. The two abstracts cited in rejection of the claims would not enable one skilled in the art to practice the subject invention, because one abstract provided insufficient guidance and the direction provided in the other was incorrect. The Examiners agreed to reconsider the rejections if these arguments were submitted in an Amendment.

The § 112 rejection will also be reconsidered in view of additional references (submitted herewith) showing that a unique antigen is identified by the monoclonal antibody of the deposited hybridoma.

The Invention

The subject invention is directed to monoclonal antibodies capable of recognizing an antigen which is found on human pluripotent lympho-hematopoietic stem cells, but not found on mature, non-malignant human myeloid or lymphoid cells. These monoclonal antibodies can be used to select stem cells from heterogeneous cell populations which contain, in addition to stem cells, mature cell types (and possibly malignant cell types). The stem cells thus selected can be used in bone marrow transplants.

The antigen recognized by the monoclonal antibodies of this invention has been designated My-10 antigen by the inventor, and subsequently CD-34 (antibody cluster designation) by the Third International Workshop on Leukocyte Differentiation. The My-10 antigen is expressed by stem cells in the undifferentiated state, but disappears as the cells differentiate and mature. Thus, antibodies to the My-10 antigen can be used for identification (and ultimately the separation) of a small number of stem cells among a very large number of mature, differentiated cells in blood or bone marrow.

Rejection Under 35 U.S.C. § 112

Claims 1-3 and 6-8 stand rejected under 35 U.S.C. § 112, first paragraph, on the ground that the disclosure is enabling only for claims limited to the monoclonal antibodies used to generate the data of the disclosure. This rejection is respectfully traversed.

As reported by Peschel, et al., at the Fourth International Conference on Leukocyte typing, p. 817, "the expression of the antigen labelled by CD34 mAb is restricted to immature human hematopoietic precursor cells, the only exception being capillary endothelial cells." Claim 2 is directed to an antibody that recognizes an antigen present on precursor cells for both myeloid and lymphoid cell types as well as on erythroid precursors. The antigen is identified by use of the antibody made by ATCC HB-8483. As reported by Civin, et al., 1989, pages 818-819 of the Report on the CD34 Cluster Workshop, presented at the Fourth International Leukocyte Typing Conference, CD34 cluster antibodies react with an antigen found on precursors to each of these cell groups.

An antibody cluster is defined by common reactivity with a single antigen. As reported in Civin, et al., (1989) a number of laboratories have confirmed that the My-10 antibody, produced by ATCC HB-8483, is specific for an epitope on the CD34 antigen, and so the My-10 antibody was the first publically disclosed antibody identified with the CD34 antibody cluster. Therefore a teaching which would enable one of ordinary skill to obtain a hybridoma secreting a monoclonal antibody specific for the antigen recognized by My-10 antibody would enable claim 7 drawn to an immortal antibody producing cell line and claim 2 drawn to the antibody produced by the cell line, respectively.

The method of producing hybridomas in order to obtain monoclonal antibodies specific for particular antigens is well known. The specification, together with the deposited hybridoma, clearly identifies the unique antigen, CD34, to be used in this

case. The specification does enable one of ordinary skill to obtain the claimed monoclonal antibodies specific for the unique CD34 antigen.

Claims 2 and 7 are fully enabled by the specification as originally filed. Applicants respectfully request that the rejection of said claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by two 1982 abstracts by Civin, et al. (AS and AT). This rejection is respectfully traversed.

While the desirability of antibodies specific for stem cells was discussed in the literature, no way of obtaining such antibodies was known prior to the subject invention. It is well settled that in order to be an anticipation, a publication must put the public in possession of the invention. In re Donohue, 207 USPQ 196 (CCPA, 1980).

While the cited abstracts provide evidence that KG1A cells are immunogenic, they do not disclose that one of the many, many antigens on the surface of KG1A cells is, in fact, peculiar to human stem cells. Further, neither abstract provides a teaching of a selection method which would enable one of ordinary skill to identify hybridomas which produce the claimed antibodies which are antibodies specific for antigens peculiar to stem cells.

Abstract AS reports monoclonal antibodies with four different specificities each unique from one another. No evidence or suggestion is provided that any of these monoclonal antibodies react with an antigen which is found on stem cells but not on mature cells. No criteria is provided to select a particular one of these monoclonal antibodies which would react with stem cells. One of the four antibodies is designated My-10, but it is taught in the abstract to be specific for an antigen with molecular weight of 95 kD. The monoclonal antibody of the subject invention is designated My-10,

but it is specific for an antigen of 115 kD (specification, p. 5, line 20; see also Civin, et al., 1989, p. 818, where multiple laboratories report the CD34 antigen to be 107-120 kD). Thus abstract AS would lead one of ordinary skill in the art to select antibodies which were specific for an antigen other than the CD34 (My-10) antigen identified by antibodies of the subject invention.

Abstract AT reports that monoclonal antibodies against KG1A cells react with ANLL cells. The abstract speculates that some of these monoclonal antibodies may react with some unidentified early progenitor cell populations, but does not provide enough information to define which cell population is referred to. There are many types of progenitor cells. Simply because an antigen is present on some progenitor does not mean that it is necessarily also present on the stem cell. Because the cell population reactive with the antibody is not defined, the abstract does not teach any method of selecting the desired antibody. Moreover, there is no indication from this reference that an antibody even exists which reacts with stem cells but not with mature cells.

In summary, neither abstract defines an immunogen, in either physical or functional terms, which could be used by one of ordinary skill to produce and select hybridomas producing monoclonal antibodies specific for antigens found on stem cells but not mature cells. Moreover, there is no teaching in either abstract that an antigen actually exists which is present on the surface of progenitors to a broad range of bone marrow cell types, but not present on mature cells. Because the Civin, et al. abstracts of 1982 do not provide a teaching which would enable one of ordinary skill in the art to produce the claimed monoclonal antibodies or hybridomas, claims 2, 4, 5, 7, 9 and 10 are not anticipated by these abstracts. Therefore, Applicant respectfully requests that the rejection of claims 2, 4, 5, 7, 9 and 10 under 35 U.S.C. § 102(b) as anticipated by references AS and AT, be withdrawn.

Rejection Under 35 U.S.C. § 103

Claims 1-10 stand rejected over Nadler in view of the known availability of the KG1A cell line. This rejection is respectfully traversed.

Nadler provides a generic screening method for selecting monoclonal antibodies on page 189-190, and while the generic methods may be used to find monoclonal antibodies specific for antigens other than those reported, Nadler provides no guidance on doing so. As discussed above, the Civin abstracts AS and AT do not provide the direction necessary in terms of an immunogen associated with stem cells or a screening method to selected monoclonal antibodies reactive with stem cells but not with mature cells. Therefore these abstracts do not overcome the deficiencies in the primary reference.

As discussed in the Amendment filed January 25, 1990, and the Declaration of Dr. Civin submitted therewith, reference AR2 is a publication by the inventor published within one year of the filing of the parent of the subject application and thus not available as a reference. While the KG1A cell line was available prior to the inventive activity of the present inventor, it was not known prior to this invention that the KG1A cell line carried an antigen which was also found on human stem cells but not found on mature human blood cells. Therefore the mere availability of the KG1A cell line is insufficient to overcome the deficiencies in the primary reference.

While Nadler teaches a generic method for obtaining monoclonal antibodies reactive with various cell surface antigens, it does not supply a sufficient teaching to allow identification of an immunogen and selection of hybridomas producing monoclonal antibodies of the subject invention, and the known availability of KG1A cell lines without identification of the unique CD34 antigen present on their surfaces does not supply the deficiency in the primary reference. Therefore, claims 2, 4, 5, 7, 9 and 10 are not

obvious over Nadler in view of these previous known cell lines. Applicants respectfully request that the rejection of said claims under 35 U.S.C. § 103 be withdrawn.

Applicant submits that claims 2, 4, 5, 7, 9 and 10 of the subject application are now in condition for allowance and respectfully requests prompt allowance of said claims.

Respectfully submitted,

By: _____
Dale H. Hoscheit
Registration No. 19,090

Banner, Birch, McKie & Beckett
One Thomas Circle, N.W.
Washington, D.C. 20005
(202) 296-5500
DHH/LHP/ceg

Dated: June 20, 1990
Docket No. 1107.021635